



In the not-distant future, there will be a new "sacred agenda" in international affairs: policies that enable rescue of the global environment. This task will one day join, and even supplant, preventing the world's incineration through nuclear war as the principal test of statecraft.

Albert Gore, speech, Global Change Conference, Smithsonian Institution and the National Academy of Sciences, 3 May 1989

## Forum

### Comprehensive Strategies Needed to Study Breast Cancer

Breast cancer strikes one out of every nine women in the United States, and there is evidence that these rates have been steadily increasing over the last 20 years. Scientists are now taking a closer look at studies which indicate that breast cancer is produced by a complex interaction of such factors as hormonal status, genetic susceptibility, environmental exposures, and dietary components.

Results of several studies conducted by Japanese and American researchers show that breast cancer rates in Japan are low (1 in 50), but rates in Japanese-American women approach those present in the U.S. population, indicating that other factors in addition to genetics play a part in whether a woman will develop breast cancer. A study reported in the *American Journal of Epidemiology* (volume 134, 1991) focusing on the effect of smoking on breast cancer rates indicated that, although there does

not appear to be an increased risk of breast cancer in women who begin smoking as adults, breast cancer risks are significantly elevated in women who begin smoking as teenagers. Similarly, a study of atomic bomb survivors from Japan revealed that adult women exposed to radiation had breast cancer rates similar to controls, but teenage girls exposed to those same levels had markedly greater breast cancer rates later in life. These findings suggest that susceptibility to cancer-promoting environmental exposures may also be age dependent.

Animal studies bear out these findings as well. Thirty-two years ago, a study by Nobel Prize winner Charles Huggins showed that administration of polycyclic aromatic hydrocarbons (PAHs) to 50-day-old female rats produced nearly a 100% incidence of mammary cancer, as opposed to a much lower incidence in younger or older rats exposed to the same doses of these chemicals. PAHs are found in urban air pollutants and cigarette contaminants. Scientists believe that exposure to carcinogens during the period of rapid proliferation of mammary cells during puberty may permit fixation of DNA damage in the genome. Subsequent exposure to ovarian hormones, such as estradiol and progesterone, which stimulate proliferation of normal breast cells, may also expand this damage, resulting in the formation of breast tumors. Evidence shows that the incidence of breast cancer is markedly reduced in women who have had their ovaries removed before 35 years of age.

In addition to the interplay among environmental exposures, genetic susceptibility, and hormonal factors, many scientists now add diet as a possible indicator of risk for breast cancer. Although this contention is widely debated, some studies have indicated a possible link between levels of dietary fat and caloric intake and the incidence of breast cancer.

The catastrophic magnitude of breast cancer is compelling researchers to develop research strategies aimed at understanding the integrated roles of all of these factors in causing and promoting breast cancer so that effective prevention and intervention approaches can be developed.

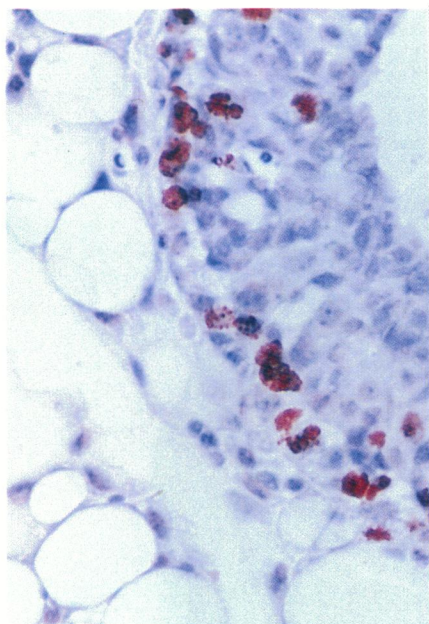
### New EPA Administrator Enters Debate over Pesticide Residues in Processed Foods

Within two weeks of the confirmation of her appointment as administrator of the Environmental Protection Agency, Carol M. Browner was faced with difficult policy decisions regarding pesticide residues in processed foods.

The EPA administers the section of the Federal Food, Drug and Cosmetic Act containing the "Delaney Clause" that prohibits any food substance that contains any cancer-causing pesticide from being processed for human consumption. The Delaney Clause was added to the Act in 1958 by the late New York Congressman James Delaney after congressional investigation of chemicals in foods and cosmetics. It was intended to protect consumers from additional cancer risks presumed to result from consumption of contaminated foods. The clause has remained in the Act ever since.

In the intervening years, analytic chemistry methods and techniques have improved dramatically, and pesticide residues can now be detected at levels below one part per trillion. At the same time, toxicologic studies have been conducted that demonstrate some level of carcinogenic activity for many agricultural chemicals. Under the Delaney Clause, no food products containing any amount of a compound that has tested positive in any laboratory study may be present in processed food. Many agricultural interests and pesticide manufacturers argue that the Delaney Clause is too restrictive and should be relaxed to permit very low levels of certain pesticides in processed foods, particularly when the toxicologic evidence of carcinogenicity from animal studies is equivocal or weak. The suggestion that "*de minimis*" levels be established for such pesticides gained support in a National Academy of Sciences report in 1989.

There is precedent for the *de minimis* approach. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) allows EPA to establish permissible trace residues of chemicals that are carcinogenic in toxicologic studies in nonprocessed,



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**Development of breast cancer.** Rapid cell division (indicated by red staining) in the developing mouse mammary gland enhances the potential for chemically induced mutations.

fresh produce marketed in the United States if the Agency determines that they do not pose an unreasonable risk.

A majority of the members of Congress and the federal courts have not been persuaded. Environmental groups and many public health experts note that the scientific base for repeal or relaxation of the Delaney Clause does not yet exist. They point out that very few pesticides have been completely tested for the full range of possible health effects, and almost nothing is known about the possible effects of consumption of the mixture of pesticide residues that could result from a diet of different processed foods containing different compounds. As a result, there is little enthusiasm in Congress for allowing any more pesticide residues in foods.

Browner was brought into the controversy when EPA staff sent her a list of 35 pesticides that EPA would ban under the Delaney Clause of the Food, Drug and Cosmetic Act. In an article in the *New York Times*, Browner was reported to support relaxing the Delaney Clause. However, she did release the list of 35 pesticides, making clear her intention to comply with the Delaney Clause. The ensuing publicity highlighted the controversy surrounding the Delaney Clause and provided interest groups with an opportunity to restate their views. Congress, however, is unlikely to intervene unless the new administration takes aggressive action and submits a legislative proposal. Such action on the part of the White House appears unlikely in the near term given the many other pressing environmental matters on the legislative agenda.

## Congress and the Clinton Administration Move to Elevate EPA to Cabinet Status

The failed Bush administration initiative to elevate the Environmental Protection Agency to cabinet status was quickly revisited by President Clinton and allies on Capitol Hill. In announcing his intention to appoint Carol M. Browner as Administrator of EPA, the President stressed that she will be treated as a member of the cabinet until his campaign pledge to make EPA the newest federal executive department is realized.

Support from Congress followed immediately. Senator John Glenn (D-Ohio), chair of the Senate Government Affairs Committee, was joined by 17 other Senators in submitting Senate Bill 171, the Department of the Environment Act of 1993. In the House of Representatives, Congressman Sherwood Boehlert (D-New York) submitted House Bill 109, which is identical to Glenn's proposal.

Before the submission of these bills, rumors of proposals for substantial restructuring of the many agencies with environmental regulatory and research programs had been circulating in the executive branch. These rumors fueled speculation that either Clinton administration officials or Congress would use the legislative process both to reorganize federal environmental programs and to elevate EPA to cabinet status. Neither has occurred. The bills now under consideration in Congress offer no substantive structural changes in either EPA or the other federal departments or agencies. Quick action on the bills is anticipated, and enactment seems assured given the wide support for a Department of the Environment and the lack of controversy in the proposals.

## National Academy of Sciences Enters Controversy on Relevance of Animal Toxicologic Studies

The National Academy of Sciences Committee on Risk Assessment Methodology issued another of its series of reports on *Issues in Risk Assessment* in February 1993. These reports have focused on the scientific methods used by toxicologists in animal studies to test chemicals and other environmental agents for adverse health effects. Such studies are critically important in providing information for use by risk assessors in evaluating the hazards to human health posed by exposure to these agents. The report focused on the "maximally tolerated dose" in animal studies designed to identify the capacity of the substance being tested to cause cancer in the animal system.

The usual practice in such toxicologic studies is to determine the dose of the substance to be studied that does not cause any acute health effects in the test animals. This dose is then given in a continuous exposure regimen to a group of healthy animals. In addition, other groups of animals are exposed to the same substance but at lower levels to determine carcinogenic potency and any dose response. These studies also include a group of animals that are not exposed to the substance for use as a control. The rationale for the use of the maximally tolerated dose includes the fact that the rodents commonly used in toxicologic research metabolize chemicals at a much higher rate than humans, and their life spans are much shorter than humans.

Some scientists believe that any carcinogenic effects noted in the group of animals exposed to the maximally tolerated dose should be discounted or ignored in extrapolating the results of the testing to humans in risk assessments. They base

their arguments on the premise that humans rarely experience long-term exposures to environmental agents at levels as high as the maximally tolerated doses established for toxicology studies and offer hypotheses for mechanisms of carcinogenicity that are unique physiologic responses to very high levels of exposure.

The majority of the National Academy of Sciences committee recommended the continued use of the maximally tolerated dose in the overall strategy for toxicologic testing. The committee recommended that additional metabolic and physiologic studies be conducted when the initial test results at the maximally tolerated dose warrant further study. One-third of the panel disagreed: They suggested that the metabolic and physiologic studies be conducted first, and the dose regimens be established on the basis of the results of this research.

The panel did agree on a number of matters. The scientists reported that if a substance is a potent cancer-causing agent in animal studies, it is likely to be toxic to people, and if the substance under test is carcinogenic at relatively low doses in animals, it has a greater likelihood of being a potent human toxicant. These points underscored the utility of toxicologic tests to determine the maximally tolerated dose as preliminary screening tests for the identification of potentially hazardous substances and the prioritization of environmental agents for further toxicological studies.

The National Academy of Sciences will continue to study and report on important issues in risk assessment. The report on issues surrounding the maximally tolerated dose and associated recommendations for additional studies of mechanisms of toxicity was issued with two other reports, one on the two-stage model of carcinogenesis and the other on a new paradigm of ecological risk assessment.

## Carnegie Commission Advocates Reorganization of Federal Environmental Research Programs

The Carnegie Commission on Science, Technology, and Government released a report, *Environmental Research and Development—Strengthening the Federal Infrastructure*, 15 December 1992. The report, drafted by a task force of senior scientists and environmental policy experts with vast experience within and outside government, called for substantial restructuring of the federal environmental research and development organizations now found in at least a dozen agencies and departments.